REMARKS/ARGUMENTS

With this amendment, claims 37-48 are pending. For convenience, the Examiner's rejections are addressed in the order presented in a November 22, 2004, Advisory Action.

I. Rejections under 35 U.S.C. §103(a)

Claims 37-48 are rejected under 35 U.S.C. §103(a) as being allegedly obvious in view of Bulow *et al.*, *TIBtech* 9:226-231 (1991); Defrees *et al.*, WO 96/32491; and the common knowledge of the art of molecular biology provided by Sambrook *et al.*, pages 7.37-7.52 (1989) in further view of Gilbert(a) *et al. Eur. J. Biochem.*, 249:187-194 (1997) and Gilbert(b) *et al. Biotech. Lett.* 19:417-420 (1997). Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143.

Applicants continue to assert that the cited references, alone or in combination, fail to teach or suggest all the elements of the claimed invention and fail to teach or suggest their combination to arrive at the claimed invention. Thus, Applicants continue to assert that a prima facie case of obviousness has not been provided in this Advisory Action or any previous Office Action.

Moreover, Applicants provide evidence of unexpected results on fusion of α-2,3-sialyltransferase and CMP-NeuAc synthetase proteins in the form of a declaration from inventor Dr. Michel Gilbert. The MPEP clearly states that evidence of unexpected results can be used to support a finding of nonobviousness of the claims. MPEP 716.01.

The Examiner appears to consider Bulow *et al.* to teach the unexpected results of the claimed fusion proteins, *i.e.*, increased activity of both the CMP-Neu5Ac synthetase and α-2,3-sialyltransferase on fusion and greatly improved solubility of the α-2,3-sialyltransferase

protein on fusion. This is incorrect. Bulow *et al.* does not teach or suggest that enzyme activity (*i.e.*, turnover number) of fusion protein components increases, relative to the unfused proteins. Nor does Bulow *et al.* teach that an insoluble protein would have markedly improved solubility on fusion to a second protein. Moreover, the deficiencies of Bulow *et al.* are not remedied by the other cited references.

With regard to the improvement in individual enzymatic activity, Bulow *et al.* teach only improvements in a coupled reaction activities, relying on *e.g.*, proximity effects for the difference between unfused enzymes and fused enzymes. Bulow *et al.* does not teach improvement in activity of individual proteins after fusion. "When corrected for the increase in molecular weight caused by the fusion, the specific activities correspond to 50-100% of those of native enzymes." *See, e.g.*, Bulow *et al.* at page 230, first full paragraph. In contrast, the specification demonstrates that the turnover rate of the unfused α-2,3-sialyltransferase is 1.4 s^{-1}, while the turnover rate of the fused α-2,3-sialyltransferase is 3.2 s^{-1}. Thus, the activity of the fused α-2,3-sialyltransferase corresponds to 229% of the activity of the unfused enzyme. The specification also demonstrates that the turnover rate of the unfused CMP-NeuAc synthetase is 31.4 s^{-1}, while the turnover rate of the fused CMP-NeuAc synthetase is 39.5 s^{-1}. Thus, the activity of the fused CMP-NeuAc synthetase corresponds to 126% of the activity of the unfused enzyme. Since Bulow *et al.* did not teach any improvement in specific activity of an individual protein on fusion, Dr. Gilbert asserts that the observed increases of 129% of α-2,3-sialyltransferase activity and 26% of CMP-NeuAc synthetase activity are unexpected.

With regard to the improvement in solubility of the α-2,3-sialyltransferase protein on fusion, Dr. Gilbert asserts that the increase in solubility after fusion is five fold that of the unfused α-2,3-sialyltransferase protein. The data to support this assertion is in the specification at page 45, lines 14-19. This improvement in solubility has the practical effect of improving efficiency of oligosaccharide production. For example, when the α-2,3-sialyltransferase/CMP-NeuAc synthetase fusion protein was used in large scale synthesis of sialyllactose, the reaction went to completion. See, *e.g.*, specification at page 48, lines 4-9.

According to the Federal Circuit, " when an applicant demonstrates substantially improved results. . . and states that the results were unexpected, this should suffice to establish

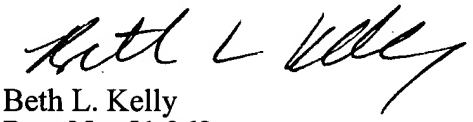
unexpected results in the absence of evidence to the contrary." *In re Soni*, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995). Applicants have submitted evidence of substantially improved results and have state that the results were unexpected. In view of the evidence submitted with this response and the arguments above, Applicants respectfully request that the rejection for alleged obviousness be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Beth L. Kelly
Reg. No. 51,868

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
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